Adverse effects of plant food supplements and plants consumed as food: Results from the poisons centres-based PlantLIBRA study

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Abstract: Plant food supplements (PFS) are products of increasing popularity and wide-spread distribution. Nevertheless, information about their risks is limited. To fill this gap, a poisons centres-based study was performed as part of the EU project PlantLIBRA. Multicentre retrospective review of data from selected European and Brazilian poisons centres, involving human cases of adverse effects due to plants consumed as food or as ingredients of food supplements recorded between 2006 and 2010. Ten poisons centres provided a total of 75 cases. In 57 cases (76%) a PFS was involved; in 18 (24%) a plant was ingested as food. The 10 most frequently reported plants were Valeriana officinalis, Camellia sinensis, Paullinia cupana, Melissa officinalis, Passiflora incarnata, Mentha piperita, Glycyrrhiza glabra, Ilex paraguariensis, Panax ginseng, and Citrus aurantium. The most frequently observed clinical effects were neurotoxicity and gastro-intestinal symptoms. Most cases showed a benign clinical course; however, five cases were severe. PFS-related adverse effects seem to be relatively infrequent issues for poisons centres. Most cases showed mild symptoms. Nevertheless, the occurrence of some severe adverse effects and the increasing popularity of PFS require continuous active surveillance, and further research is warranted.

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Short title: Adverse effects of PFS and plants consumed as food

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Adverse reactions; toxicity; botanicals; plants; nutritional supplements; poisons centres.

Abstract

Objective:

Plant Food Supplements (PFS) are products of increasing popularity and wide-spread distribution. Nevertheless, information about their risks is limited. To fill this gap, a poisons centres-based study was performed as part of the EU project PlantLIBRA.

Methods:

Multicentre retrospective review of data from selected European and Brazilian poisons centres, involving human cases of adverse effects due to plants consumed as food or as ingredients of food supplements recorded between 2006 and 2010.

Results:

10 poisons centres provided a total of 75 cases. In 57 cases (76%) a PFS was involved; in 18 (24%) a plant was ingested as food. The 10 most frequently reported plants were *Valeriana officinalis, Camellia sinensis, Paullinia cupana, Melissa officinalis, Passiflora incarnata, Mentha piperita, Glycyrrhiza glabra, Ilex paraguariensis, Panax ginseng,* and *Citrus aurantium*. The most frequently observed clinical effects were neurotoxicity and gastro-intestinal symptoms. Most cases showed a benign clinical course; however, five cases were severe.

Conclusions:

PFS-related adverse effects seem to be relatively infrequent issues for poisons centres. Most cases showed mild symptoms. Nevertheless, the occurrence of some severe adverse effects and the increasing popularity of PFS require continuous active surveillance, and further research is warranted.

1. Introduction

In the last two decades, the use of dietary supplements has increased dramatically all over the world. Changes in the legislation of medications and related products lead to an expansion of the markets for dietary supplements and allowed more intensive marketing (Denham, 2011; Miroddi, 2013; Silano, 2011; Vargas-Murga, 2011), resulting in a growing awareness and information of the population about health aspects. The rising significance of health issues in daily life, together with an increased possibility and tendency to self-medicate, and the aging of the population seem to be the major reasons for the success of the dietary supplements (Kennedy, 2005; Peters, 2003). Additional factors that promote the consumption of products of plant origin include the belief that botanicals are natural and therefore safe and the mistrust in conventional medications (Egan, 2011; Lynch, 2007; Marinac, 2007).

Food supplements with botanical ingredients, also called plant food supplements (PFS), cover a broad field of indications and therefore a wide range of plants are involved. Some preparations contain only one ingredient, which can consist of an extract (or concentrate) of a single plant or a specific plant compound (e.g. caffeine). Other PFS are a combination of several plants. In case of adverse effects, the complex nature of these ingredients and products makes it difficult to identify the causative component.

Along with the global spreading and the increasing use of PFS, scientific research on these products was intensified. However, clinical data on adverse effects of PFS are scarce and the literature mainly consists of case reports or case series on single plants (Di Lorenzo, 2015). The issue of underreporting is

particular relevant in this area and partially explains paucity of data on adverse effects to these products (Geller, 2015; Kennedy, 2005).

The occurrence of some severe incidents after the intake of PFS (Palmer, 2003; Vassilev, 2009; Vitalone, 2011), demonstrated the need for additional studies on PFS-related adverse effects. For these reasons, the European Community's Seventh Framework Programme funded PlantLIBRA project (www.plantlibra.eu) also comprised research on the adverse effects profile of PFS and plants consumed as food (Bucchini, 2011).

The aim of this study was to identify plants commonly involved in adverse reactions related to the intake of PFS and of plants consumed as food, and to describe the type and severity of associated signs and symptoms by analysing data collected by poisons centres.

2. Methods

2.1 Study design

Through a multicentre retrospective review of data from European and Brazilian poisons centres, documented human adult and pediatric cases (children defined as ≤ 16 years) of adverse effects related to the intake of PFS or plants consumed as food were collected for the period 2006 – 2010. The inclusion of Brazil in a European study is due to the fact that the University of San Paulo was one of the extra-European PlantLIBRA partners, as required by the specific project call.

2.2 Inclusion and exclusion criteria

The following criteria had to be met for reported cases to be included in the study:

- Exposure to an agent categorized as PFS by the reporting poisons centre or exposure to a plant listed in an annex of the study protocol (the plant list can be accessed online as supplementary data, table A). This list mainly represents plants commonly used in PFS.
- Symptoms/signs of an adverse effect;
- Complete observation (i.e. medical follow-up covering the entire course of illness related to the exposure, until the resolution of symptoms or until stable presentation of sequelae);
- Confirmed or probable causal relationship between exposure and clinical effect(s). Causality assessment was based on the World Health Organisation Uppsala Monitoring Centre (WHO-UMC) standardised case causality assessment criteria originally developed for the assessment of adverse drug reactions (WHO, 2015) and included an adequate temporal relationship between exposure and symptoms, absence of other exposures or underlying diseases that can also explain the symptoms, and the presence of symptoms which are described for the substance in question or are plausible from a toxicodynamic point of view.

Exclusion criteria were:

- Asymptomatic exposures;

- Ingestion of the PFS/plant for other reasons than for nutrition or for a health benefit (e.g. child ingesting a plant accidentally; misidentification of plants);
- Ingestion of a plant (as food), that is not on the list;
- Ingestion outside the study period.

Each case was reviewed in detail and independently assessed by an expert panel at the Swiss National Poisons Centre, Tox Info Suisse, consisting of a pharmacist with expertise in plants, and a senior clinical pharmacologist and toxicologist with additional qualifications in general internal medicine. Any disagreement in case assessment was resolved by consensus.

2.3 Data collection and study population

Poisons centres were identified and contacted using the EAPCCT network (European Association of Poisons Centres and Clinical Toxicologists). The poisons centres were required to provide anonymized data – including age, sex, and weight of the patient, ingested substance and, if available, dose, type of symptoms/signs, laboratory values and causal relationship, severity of symptoms and signs (graded according to the Poisoning Severity Score, PSS (Persson, 1998)), therapeutic interventions and, if applicable, decontamination procedures performed with time between ingestion and decontamination – in a standardized exchange spreadsheet format. Data had to be translated into English; however Italian, Spanish, French, and German were also accepted due to language competencies within the Swiss National Poisons Centre.

66 requests for participation in the study were sent to European and Brazilian poisons centres. Of the 41 (62%) poisons centres who answered, 10 were able to provide a total of 426 cases. 351 (82%) of these had to be excluded because they did not meet the inclusion criteria (i.e., insufficient causal relationship between ingested plant/PFS and observed symptoms and signs, asymptomatic ingestion, product not a PFS or plant not on the list, wrong circumstances of ingestion (e.g. child ingesting a plant accidentally), year of occurrence not within the study period), leaving 75 (18%) cases of adverse effects which were available for analysis.

2.4 Data processing and analysis

Since not all centres classify the severity of signs and symptoms in the same way, the cases were re-evaluated according to the Poisoning Severity Score (PSS) developed by the European Association of Poisons Centres and Clinical Toxicologists, the International Programme on Chemical Safety, and the European Commission (Persson, 1998). The severity of symptoms of individual patients was classified as "minor" if only mild, transient and spontaneously resolving symptoms/signs were present, as "moderate" if at least one pronounced or prolonged symptom/sign was recorded, as "severe" if at least one severe or life-threatening symptom/sign was observed, or as "fatal", if the ingestion of the PFS or plant was the recorded cause of death.

Data from the centres were merged into one single standardized Excel spreadsheet (Microsoft Excel 2010, Microsoft Corporation, Redmond, USA) and categorized into age groups, type of product, organ system involved, and

severity of symptoms and signs. For the analyses of the relationships between PFS/plants and symptoms/signs, data were exported into an Access database (Microsoft Access 2010, Microsoft Corporation, Redmond, USA). Descriptive statistics were used to analyze grouped data.

2.5 Ethical approval

No ethics approval was required for this study according to a statement of the cantonal ethics committee Zurich. Each of the participating poisons centres was required to investigate whether or not a local ethics committee/institutional review board approval was required. The answers, and if applicable the local ethics committee approval, were transmitted to the Swiss National Poisons Centre, Tox Info Suisse. The procedure was surveyed by the ethics advisor of the PlantLIBRA project.

2.6 Data protection issues

Analyses were performed with completely anonymized data. Information was accessed and handled by study members only.

3. Results

3.1 Patient characteristics and severity of signs and symptoms

The 75 cases included in the study originated from all over Europe (Finland 9 cases, France 31, Germany 4, Italy 13, Serbia 4, Sweden 5, Switzerland 5) and Brazil (4). Demographic characteristics of the patients were as follows: 68 adults (91%) with a mean age of 41.7 years (SD 18.8, median 40.0, range 16-92; age unknown in six cases) and seven children (9%) with a mean age of 11.4 years (SD 5.4, median 15, range 2-15). Both genders were almost equally represented among adults and children, in total there were 41 females (55%) and 34 males (45%).

Most cases showed a benign clinical course (table 1). Children mainly developed minor signs and symptoms, and there were no severe cases among this age group. Adults older than 65 showed a tendency towards more moderate and severe clinical courses compared to younger patients. No fatal outcome was observed.

3.2 Involved plants/PFS and severity of signs and symptoms

In 57 cases (76%) a PFS was involved, and in 18 (24%) a plant was ingested as food (table 1). The number of involved PFS containing only one ingredient ("PFS mono") was comparable to that with more than one ingredient ("PFS multi"). PFS with more than one ingredient were more frequently associated with moderate and severe clinical courses (33.3%) compared to PFS with only one ingredient (10.0%).

Plants, as ingredients of PFS or consumed as food, involved in three or more cases are listed in table 2. Plants most commonly ingested as PFS were *Valeriana officinalis* L.*, Camellia sinensis* (L.) Kuntze*, Paullinia cupana* Kunth*,*

Melissa officinalis L.*,* and *Mentha piperita* L.*;* plants most commonly consumed as food were *Glycyrrhiza glabra* L.*, Cynara scolymus* L.*, Allium ursinum* L.*,* and *Taraxacum officinale* L.. The severity of signs and symptoms in relation to all plants involved in the cases of adverse effects due to the ingestion of a PFS or a plant consumed as food is shown in table 3.

3.3 Organ systems involved and observed signs and symptoms

3.3.1 General evaluation

In 59 (79%) of the 75 patients only one organ/organ system was involved; 14 patients had two organs/systems involved, and two patients had more than two organs/systems involved. The most frequently involved organ system was the nervous system (n = 34), followed by the gastrointestinal system (n = 27), the cardiovascular system (n = 13), skin/mucosa (n = 8), the liver (n = 4), the respiratory system (n = 2), the kidney (n=1), and other organ systems (n= 5). 35 patients showed one symptom, 27 patients two symptoms, 10 patients three symptoms, two patients four symptoms, and one patient five symptoms. All signs and symptoms observed in the patients are listed in table 4.

3.3.2 Analysis for individual plants

An overview of the reported signs and symptoms in relation to the plants involved in all cases of ingestion of PFS or plants consumed as food can be accessed online as supplementary data (table B).

3.4 Severe cases

There were five severe cases (table 5); in three of these, a multi-ingredient PFS was involved. In a 72-year-old patient consuming *Glycyrrhiza glabra* L. and *Mentha piperita* L. as an infusion in a high dose, a hypertensive crisis and severe hypokalemia were observed. In another case, a 30-year-old man was using a product containing *Citrus aurantium* L.*, Camellia sinensis* (L.) Kuntze*, Paullinia cupana* Kunth*,* and *Coleus forskohlii* (Willd.) Briq., which he combined with a product containing *Rhodiola rosea* L. to lose weight. He had a weight loss of 18 kg in two months, and suffered a myocardial infarction during sexual activity. He recovered completely. In a third case, a 40-year-old patient ingested a PFS containing *Panax ginseng* C.A.Mey.*, Paullinia cupana* Kunth*, Ilex paraguariensis* A.St.-Hil.*, Lepidium meyenii* Walp, *Turnera diffusa* Willd. ex Schult.*, Avena sativa* L., and *Capsicum sp.* to increase his sexual potency. A few hours after the ingestion of a single recommended dose he suffered a transient ischemic attack (TIA). A rechallenge with the product provoked the recurrence of the transient ischemic attack, which resolved without specific treatment. In the two other cases, both patients showed a severe allergic reaction.

4. Discussion

In this study, adverse effects due to the ingestion of PFS or plants consumed as food seem to be infrequent issues for poisons centres; a finding that is supported by other studies. An analysis of calls involving the ingestion of a single medication reported to a poisons centre revealed that 3.4% were related

to adverse drug reactions and of these only 4.7% were caused by the group of dietary supplements/herbals/homeopathics (Vassilev, 2009). In a prospective poisons centre study, only 0.4% of the calls concerned dietary supplements, of which 33% were due to adverse effects (Haller, 2008). Since the consumption of dietary supplements is wide-spread, it is plausible that adverse effects occur regularly, as has been recently shown by Geller et al. (Geller, 2015), but are probably detected only to a small extent by poisons centres or physicians. People not thinking of poisons centres as information source or not reporting their use of dietary supplements to the physician might explain these observations; this has been confirmed by other studies (Kennedy, 2005; Wu, 2011). A study investigating the safety of phytomedicines (Cuzzolin, 2006), found that about half of the interviewed women attending an urban university hospital were consuming a PFS and 10% of them reported adverse effects. In 62% the adverse effects were not communicated to the doctor. In addition, consumers might not be aware that they are suffering from adverse effects due to herbal supplements.

This study analyzed two situations in which plant material was ingested: on the one hand the ingestion of a plant in form of a preparation (PFS) with the purpose to maintain health, and on the other, the consumption of a plant as food. Between these two situations there were considerable differences concerning the involved plants and, accordingly, the observed signs and symptoms. Consumption of plants as food mainly involved a single plant and caused gastrointestinal symptoms, allergic reactions, and electrolyte changes, whereas the ingestion of PFS involved many different symptoms due to the

large diversity of plants and the concurrent ingestion of multiple plants. Although the two situations differ considerably, information about symptoms related to the ingestion of a single plant as food might give an indication about the possible toxicity of a PFS containing the same plant.

In this study gastrointestinal and neurological symptoms were the clinical effects most frequently observed, which is in accordance with data from the Italian pharmacovigilance centre on spontaneously reported adverse effects related to natural health products (including homeopathics) (Menniti-Ippolito, 2008). Data on complementary medicines from pharmacovigilance centres in Sweden and Singapore showed different results. In the Singapore database mostly endocrine and nervous system disorders were recorded (Patel, 2012), whereas in Sweden skin and hypersensitivity reactions predominated (Jacobsson, 2009). Part of these differences can be explained by the type of institution which performed the study: pharmacovigilance centres focus on adverse reactions to drugs ingested in therapeutics doses, whereas poisons centres mostly deal with overdoses of drugs and other substances. The fact that skin reactions predominated among the adverse effects to natural health products in the Swedish study is in line with data from the WHO adverse drug reactions database, where skin reactions were the most frequently registered symptoms associated with the use of herbal medicines (Farah, 2000). In the Singapore study, many cases of adulteration (with pharmaceutical substances) were reported and the involved substances rather than the plants were responsible for the adverse effects (e.g. endocrine disorders). The quality of the involved plant material is a general issue when it comes to the use of PFS. Lack of

standardization and contamination with other plants during preparation, together with no or poor quality control may lead to adverse effects in case of consumption (Soares Neto, 2013) and could have also contributed to the adverse effects observed in our study.

Hepatotoxicity is an important issue when investigating the safety of medications, and many herbal medications do affect the liver (Bunchorntavakul, 2013; Stickel, 2005; Teschke, 2012). Nevertheless, in this study there were only few reports of hepatotoxicity (4 of 75 cases), and this is in contrast to the literature. The plants associated with hepatic signs and symptoms in this study included *Angelica archangelica* L., *Camellia sinensis* (L.) Kuntze, *Carum carvi* L., *Crithmum maritimum* L., *Dioscorea villosa* L., *Fucus vesiculosus* L., *Glycine max* (L.) Merr., *Hibiscus sabdariffa* L., *Mentha piperita* L., and *Opuntia ficus-indica* (L.) Mill.. Although reports and experimental studies on hepatotoxicity of *Camellia sinensis* (L.) Kuntze (Bunchorntavakul, 2013; Mazzanti, 2009), *Dioscorea villosa* L. (Wojcikowski, 2008), and *Mentha piperita* L. (Akdogan, 2004) exist, the design of the present study does not allow to add further evidence, particularly if the plant was part of a multi-ingredient product. In addition, a causality assessment according to RUCAM (Roussel Uclaf Causality Assessment Method), which is the reference method for evaluating drug and herb induced liver injury (Danan, 2016), was not possible due to incomplete case information. This is for example the case for *Dioscorea villosa* L., which was involved in two of the four cases of hepatotoxicity. However, as the PFS included multiple ingredients and as some analytical data were missing, a

definitive causal relationship could not be established. Nevertheless, this plant deserves particular attention and further investigation is warranted.

Most cases in this study showed mild symptoms and a benign clinical course, which is consistent with other studies from poisons centres evaluating adverse effects related to herbal remedies and dietary supplements (Haller, 2008; Yang, 2002), where most adverse effects were mild and severe outcomes were rare. In contrast, the adverse effects described in the Italian pharmacovigilance study were associated with a rather high need for hospitalization (Menniti-Ippolito, 2008), an observation they explain by a greater attention to complete drug history in patients with serious reactions. In our study, there seemed to be more severe courses when a multi-ingredient PFS or a plant consumed as food were involved, as compared to the ingestion of a single-ingredient PFS. The symptoms most commonly recorded in the moderate cases of this study were - apart from unspecific gastrointestinal symptoms - edema and hypokalemia, sometimes accompanied by hypertension or ECG changes. In all of these cases *Glycyrrhiza glabra* L. was involved. These observations correspond well to the known effects of the plant, which affects the electrolyte balance (Isbrucker, 2006; Olukoga, 2000).

The plant most commonly involved in cases of adverse effects related to the ingestion of PFS or plants consumed as food was *Valeriana officinalis* L.. The adverse reactions most frequently observed with this plant in this study, i.e. somnolence, drowsiness, and gastrointestinal symptoms, are also described in the literature (Taibi, 2007), and the neurological symptoms are very well explained by valerian's properties as relaxant and sleep aid. Valerian was

usually the only component of the PFS ingested. This suggests a probable causal relationship between the symptoms and the plant.

Products containing widely-used plants for weight loss such as *Camellia sinensis* (L.) Kuntze*, Ephedra distachya* L.*, Hoodia gordonii* (Masson) Sweet ex Decne.*, Citrus aurantium* L.*, Garcinia cambogia* (Gaertn.) Desr. were only rarely recorded, although they are marketed as highly effective. Reasons for this observation might be the poor availability in shops due to legal restrictions based on their negative safety profile or the fear of serious side effects (i.e. cardiotoxicity), which are known for some of these plants (Vitalone, 2011).

Some other plants reported to be most frequently used as supplements in the literature, including *Panax ginseng* C.A.Mey., *Echinacea sp.*, *Ginkgo biloba* L., *Hypericum perforatum* L., *Allium sativum* L., and *Serenoa repens* (W.Bartram) Small (Kennedy, 2005; Marinac, 2007; Wu, 2011), were only rarely involved in the cases of this study. The same is true for plants contained in supplements enhancing athletic performance and aphrodisiacs (e.g. *Coleus forskohlii* (Willd.) Briq.*, Schisandra chinensis* (Turcz.) Baill.*, Tribulus terrestris* L.*, Pausinystalia yohimbe* (K.Schum.) Pierre ex Beille, *Epimedium grandiflorum* C.Morren, *Trigonella foenum-graecum* L., *Lepidium meyenii* Walp, *Turnera diffusa* Willd. ex Schult.) (Rowland, 2003). This may be due to the fact that some products containing these plants are classified as pharmaceuticals and not as PFS and were therefore not included in the study.

Limitations

The interpretation of the findings of this study is mainly limited by the retrospective nature of the study design with the related incompleteness of data and lack of uniform data classification. This is for example the case for the ingested dose of a PFS or a plant, which could not always be recorded or specified in detail. In addition, this is the reason why causality assessment of hepatotoxicity cases according to RUCAM (Danan, 2016) was not possible.

A further limitation is related to the object of the study and to the fact that there is a lack of uniform categorization of PFS among different countries. The legal status of a herbal preparation depends on the law of the specific country, meaning that a preparation can be classified as a supplement in one country, as a (traditional) medicinal product in another, and as a pharmaceutical in a third one (Egan, 2011; Silano, 2011). Also the wide range of different terminology used for PFS, which are interchangeably referred to in the literature as ‘‘plant foods’’, ‘‘plant extracts’’, ‘‘botanicals’’, ‘‘herbals’’ and/or ‘‘herbs’’ (Egan, 2011) adds to the complexity of the subject.

Furthermore, it is known from the literature that data from poisons centres are subject to reporting bias (Hoffman, 2007) and it is plausible that delayed effects and chronic toxicity were underrepresented. It is also known that patients tend to underreport the use of PFS and the magnitude of their use is underrecognized by physicians (Cuzzolin, 2006; Kennedy, 2005; Wu, 2011). In addition, our strict inclusion criteria led to small case numbers, especially for some PFS/plants. However, we are convinced that these restrictions were necessary to be able to interpret the findings properly. Due to the limited

number of cases involving children, the results regarding this population should be interpreted with particular caution.

The fact that a large diversity of plants was involved in many documented cases with adverse effects is an important limitation regarding the risk assessment of single plants and the establishment of a causal relationship between a plant and an adverse effect.

5. Conclusions

PFS-related adverse effects seem to be relatively infrequent issues for poisons centres and most cases in this study showed mild symptoms and a benign clinical course. Nevertheless, the occurrence of some severe adverse effects and the increasing popularity of PFS together with the issue of underreporting, require continuous active surveillance, especially of possible vulnerable groups such as the elderly. Further research is warranted to validate the preliminary results of this study, and a multidisciplinary approach with an international perspective should be prioritized.

Conflicts of interest

The authors report no declarations of interest. The authors alone are responsible for the content and writing of the paper.

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Table 1: Severity of signs and symptoms according to PSS in relation to patients' characteristics, and the product (PFS/plant). For PFS, the number of ingredients is reported (multi: >1 ingredient, mono: 1 ingredient).

	SEVERITY			
	Minor	**Moderate**	**Severe**	**Total**
PATIENT				
Adult	***50***	***13***	***5***	***68***
Female	27	10		37
Male	23	3	5	31
Child	***6***	***1***	***0***	***7***
Female	3	1		4
Male	3			3
Total	**56**	**14**	**5**	**75**
PRODUCT				
PFS	***45***	***8***	***4***	***57***
Multi	18	6	3	27
Mono	27	2	1	30
Plant	***11***	***6***	***1***	***18***
Total	**56**	**14**	**5**	**75**

Table 2: The 15 plants (as ingredients of PFS or consumed as food) involved in three or more cases of adverse effects. (Caffeine is listed because it is a relevant ingredient in many PFS and often it is added to increase the caffeine content of the product)

Plant / **Ingredient** **Latin name**	**Common name**	**As Food**	**In PFS**	**Total**
Valeriana officinalis L.	Valerian	1	22	23
Camellia sinensis (L.) Kuntze	Green tea	1	9	10
Melissa officinalis L.	Lemon balm		7	7
Mentha piperita L.	Peppermint		7	7
Passiflora incarnata L.	Passionflower	1	6	7
Paullinia cupana Kunth	Guarana		7	7
Glycyrrhiza glabra L.	Licorice	5	1	6
Ilex paraguariensis A.St.-Hil.	Yerba mate		6	6
Caffeine			5	5
Panax ginseng C.A.Mey.	Ginseng		5	5
Citrus aurantium L.	Bitter orange		4	4
Cynara scolymus L.	Artichoke	4		4
Dioscorea villosa L.	Wild yam		4	4
Allium ursinum L.	Wild garlic	3		3
Carum carvi L.	Caraway		3	3
Taraxacum officinale L.	Common dandelion	2	1	3

Table 3: Severity of signs and symptoms in relation to all 58 different plants consumed as ingredients of PFS or as food with the corresponding number of cases.

Plant / Ingredient			**Severity**			
Latin name	**Common name**	**Family**	**Minor**	**Moderate**	**Severe**	**Total**
Achyranthes aspera L.	Prickly chaff flower	Amaranthaceae		1		1
Aesculus hippocastanum L.	Horse chestnut	Sapindaceae	1			1
Allium ursinum L.	Wild garlic	Amaryllidaceae	3			3
Aloe vera (L.) Burm.f.	Aloe	Xanthorrhoeaceae	1			1
Ananas comosus (L.) Merr.	Pineapple	Bromeliaceae		1		1
Angelica archangelica L.	Garden angelica	Apiaceae		2		2
Areca catechu L.	Betel nut tree	Arecaceae		1		1
Avena sativa L.	Oat	Poaceae			1	1
Caffeine			5			5
Camellia sinensis (L.) Kuntze	Green tea	Theaceae	6	3	1	10
Capsicum annuum L.	Pepper	Solanaceae	1	1		2
Capsicum sp.	Peppers	Solanaceae			1	1
Carum carvi L.	Caraway	Apiaceae	1	2		3
Cassia angustifolia M.Vahl	Tinnevelly senna	Leguminosae	2			2
Citrus aurantium L.	Bitter orange	Rutaceae	3		1	4
Citrus limon (L.) Osbeck	Lemon	Rutaceae	1			1
Citrus sp.	Citrus fruit	Rutaceae	1			1
Cola nitida (Vent.) Schott & Endl.	Kola nut	Malvaceae	1	1		2
Coleus forskohlii (Willd.) Briq.	Indian coleus	Lamiaceae	1		1	2
Commiphora mukul (Hook. ex Stocks) Engl.	Guggul	Burseraceae		1		1
Crataegus monogyna Jacq.	Common hawthorne	Rosaceae	1			1
Crithmum maritimum L.	Sea fennel	Apiaceae		2		2
Cuminum cyminum L.	Cumin	Apiaceae	1			1
Cynara scolymus L.	Artichoke	Compositae	3		1	4
Dioscorea villosa L.	Wild yam	Dioscoreaceae		4		4
Echinacea pallida (Nutt.) Nutt.	Pale purple coneflower	Compositae	2			2
Eleutherococcus senticosus (Rupr. & Maxim.) Maxim.	Siberian ginseng	Araliaceae		1		1
Ephedra sp.	Ephedra / Ma Huang	Ephedraceae	1			1
Fucus vesiculosus L.	Bladderwrack	Fucaceae		2		2
Garcinia sp.	Garcinia	Clusiaceae	1			1
Ginkgo biloba L.	Ginkgo	Ginkgoaceae		2		2
Glycine max (L.) Merr.	Soybean	Leguminosae	1		1	2
Glycyrrhiza glabra L.	Licorice	Leguminosae	1	4	1	6
Harpagophytum procumbens (Burch.) DC. ex Meisn.	Devil's claw	Pedaliaceae	1			1
Hibiscus sabdariffa L.	Roselle	Malvaceae		2		2
Hypericum perforatum L.	St. John's wort	Hypericaceae	1			1
Ilex paraguariensis A.St.-Hil.	Yerba mate	Aquifoliaceae	4	1	1	6
Illicium verum Hook f.	Star anise	Schisandraceae	1			1
Lepidium meyenii Walp	Maca	Brassicaceae			1	1
Melissa officinalis L.	Lemon balm	Lamiaceae	7			7

Mentha piperita L.	Peppermint	Lamiaceae	6		1	7
Ocimum basilicum L.	Basil	Lamiaceae	1			1
Opuntia ficus-indica (L.) Mill.	Prickly pear cactus	Cactaceae		2		2
Panax ginseng C.A.Mey.	Ginseng	Araliaceae	3	1	1	5
Passiflora incarnata L.	Passionflower	Passifloraceae	7			7
Paullinia cupana Kunth	Guarana	Sapindaceae	4	1	2	7
Pausinystalia yohimbe (K.Schum.) Pierre ex Beille	Yohimbe	Rubiaceae	1			1
Piper nigrum L.	Black pepper	Piperaceae	1			1
Punica granatum L.	Pomegranate	Lythraceae	1			1
Rhamnus purshianus DC.	Cascara buckthorn	Rhamnaceae	1			1
Rhodiola rosea L.	Golden root	Crassulaceae			1	1
Salix alba L.	White willow	Salicaceae	2			2
Taraxacum officinale (L.) Weber ex F.H.Wigg	Common dandelion	Compositae	1	2		3
Theobroma cacao L.	Cocoa tree	Malvaceae	1			1
Turnera diffusa Willd. ex Schult.	Damiana	Passifloraceae			1	1
Vaccinium myrtillus L.	Common bilberry	Ericaceae	1			1
Valeriana officinalis L.	Valerian	Caprifoliaceae	23			23
Vitis vinifera L.	Grape vine	Vitaceae	1	1		2
Withania somnifera (L.) Dunal	Indian ginseng	Solanaceae		1		1
Total			**106**	**39**	**16**	**161**

Table 4: Observed signs and symptoms in the 75 patients with adverse effects after the ingestion of a PFS or a plant as food.

Signs / symptoms	N	Signs / symptoms	N
Nervous system		**Skin / Mucosa**	
Drowsiness	16	Skin or mucosa irritation	5
Somnolence	8	Angioedema	2
Dizziness	7	Urticaria	2
Headache	5	**Liver**	
Restlessness	2	Hepatitis	3
Tremor	2	Elevated liver enzymes	1
Transient ischemic attack	1	Icterus	1
Gastrointestinal system		**Respiratory system**	
Nausea	14	Respiratory insufficiency	2
Vomiting	14	**Kidney**	
Abdominal pain	13	Renal insufficiency	1
Diarrhea	11	**Other**	
Cardiovascular system		Hypokalemia	3
Tachycardia	5	Edema	2
Hypertension	4	Miosis	1
ECG changes	3		
Chest pain	2		
Hypotension	1		
Myocardial infarction	1		

Table 5: Plants/PFS involved and signs/symptoms observed in the five severe cases

Case	Age / Gender	Plant / PFS	Product form	Quantity	Duration of use	Latency of symptoms	Symptoms	Causality
1	72 y/o male	*Glycyrrhiza glabra* L., *Mentha piperita* L.	Tea	8 tea bags/ d	3 months	1 months; hospitalization after 3 months	Disorientation; Hypertensive crisis (210/90 mm Hg) and severe hypokalemia (1.7 mEq/L)	Probable
2	30 y/o male	*Citrus aurantium* L., *Camellia sinensis* (L.) Kuntze, *Paullinia cupana* Kunth, *Coleus forskohlii* (Willd.) Briq., *Rhodiola rosea* L.	Capsules and tablets (*Rhodiola rosea*)	Unknown	> 2 months	Unknown	Myocardial infarction	Probable; unlikely for *Rhodiola rosea*
3	40 y/o male	*Avena sativa* L., *Capsicum sp., Ilex paraguariensis* A.St.-Hil., *Lepidium meyenii* Walp, *Panax ginseng* C.A.Mey., *Paullinia cupana* Kunth, *Turnera diffusa* Willd. ex Schult.	Tablets	4 tablets	Once	Few hours	Transient ischemic attack	Certain (positive rechallenge)
4	57 y/o male	*Glycine max* (L.) Merr.	Soybean powder (Herbalife®) diluted in soybean milk	1 glass	9 days	30 min after last exposure	Angioedema	Certain (positive rechallenge)
5	41 y/o male	*Cynara scolymus* L.	Artichoke as food	Unknown	Once	10 min	Anaphylaxis	Probable